

We claim:

1. A method of sequence specific recombination of DNA in a eukaryotic cell, comprising
 - 5 a) introducing a first DNA sequence into a cell,
 - b) introducing a second DNA sequence into a cell, and
 - c) performing the sequence specific recombination by a bacteriophage lambda integrase Int.
- 10 2. Method of sequence specific recombination of DNA in a eukaryotic cell having a first DNA sequence in its genome, either naturally occurring or being introduced previously by DNA recombination, comprising the steps b) and c) defined in claim 1.
3. Method according to claim 1 or 2, wherein said first DNA sequence comprises an
15 *attB* sequence according to SEQ ID NO:1 or a derivative thereof and said second DNA sequence comprises an *attP* sequence according to SEQ ID NO:2 or a derivative thereof.
4. Method according to claim 1 or 2, wherein said first DNA sequence comprises an
20 *attL* sequence according to SEQ ID NO:3 or a derivative thereof and said second DNA sequence comprises an *attR* sequence according to SEQ ID NO:4 or a derivative thereof, wherein in step c) additionally a Xis factor is present.
5. Method according to anyone of claims 1 to 4, wherein additionally a third or a third and fourth DNA sequence comprising an Int gene or an Int gene and a Xis factor
25 gene, respectively, is introduced into the cell.
6. Method according to claim 5, said third or said third and/or fourth DNA sequence further comprising a regulatory DNA sequence effecting a spatial and/or temporal expression of the Int gene and/or the Xis factor gene.
- 30 7. Method according to anyone of claims 1 to 6, wherein said Int is a modified integrase.

8. Method according to claim 7, wherein said modified Int is Int-h or Int-h/218.
9. Method according to anyone of claims 1 to 8, wherein in step c) additionally an "integration host factor" (IHF) is involved.
- 5 10. Method according to anyone of claims 1 to 9, said first and/or second DNA sequence further comprising DNA sequences effecting an integration of said first and/or second DNA sequence into the genome of the eukaryotic cells by homologous recombination.
- 10 11. Method according to anyone of claims 1 to 10, said first and/or second DNA sequence further comprising a nucleic acid sequence coding for a polypeptide of interest.
12. Method according to claim 11, wherein said polypeptide of interest is a structural protein, an endogenous or exogenous enzyme, a regulatory protein or a marker protein.
- 15 13. Method according to anyone of claims 1 and 3 to 12, wherein said first and second DNA sequence are introduced into the eukaryotic cell on the same DNA molecule.
- 20 14. Method according to anyone of claims 1 to 13, wherein said eukaryotic cell is a mammalian cell.
15. Method according to claim 14, wherein said mammalian cell is a human, simian, mouse, rat, rabbit, hamster, goat, bovine, sheep or pig cell.
- 25 16. Method according to anyone of claims 1 to 3 and 5 to 15, further comprising d) performing after a first sequence specific recombination of DNA according to the steps a) to c) or a) and b) without a Xis factor a second sequence specific recombination of DNA by an Int and a Xis factor.
- 30 17. Method according to claim 16, further introducing a further DNA sequence into said cells, the further DNA sequence comprising a Xis factor gene.

18. Method according to claim 17, wherein said further DNA sequence comprises further a regulatory DNA sequence effecting a spatial and/or temporal expression of said Xis factor gene.

5 19. The use of an *attB* sequence according to SEQ ID NO:1 or a derivative thereof and an *attP* sequence according to SEQ ID NO:2 or a derivative thereof, or an *attL* sequence according to SEQ ID NO:3 or a derivative thereof and an *attR* sequence according to SEQ ID NO:4 or a derivative thereof in a sequence specific recombination of DNA in eukaryotic cells.

10

20. Nucleic acid sequence according to SEQ ID NO:5 or a derivative thereof.

15

21. Vector, comprising a nucleic acid sequence according to SEQ ID NO:5 or a derivative thereof and a further nucleic acid sequence coding for a therapeutic gene or a DNA fragment thereof.

22. Vector according to claim 21, wherein said therapeutic gene is the CFTR gene, ADA gene, LDL receptor gene, β globin gene, Factor VIII gene or Factor IX gene, alpha-1-antitrypsin gene or the dystrophin gene or a gene fragment of one of said genes.

20

23. Vector according to claim 21 or 22, wherein said further nucleic acid sequence comprises further expression and/or transcription elements.

25

24. Vector according to anyone of claims 21 to 23 for the use as a medicament in the human or veterinary medicine.

25. Use of a vector according to anyone of claims 21 to 23 for the manufacture of a medicament for the somatic gene therapy.

30

26. Eukaryotic cell, obtainable by subjecting said eukaryotic cell of claim 1 or 2 to the method according to anyone of claims 1 to 18.

27. Transgenic organism comprising at least one cell according to claim 26.

28. The organism according to claim 27, wherein said organism is a mouse, rat rabbit or hamster.

ADD
A27

25137992.1